What’s New in Urology

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Editor in Chief Journal of Urology
Department of Urology
Topics

- Overactive Bladder /Incontinence
- BPH
- Androgen deficiency/replacement
- ED
- Uncomplicated UTI
- Female urology
- Stone Disease
- Prostate Cancer
- Bladder Cancer
- Kidney Cancer
• Help manage your patients with common GU conditions better
• See if your urology colleagues practicing contemporary, data driven care
What is overactive bladder? (OAB)

• Experts debate definition ¹
  – ‘02 ICS “Urgency with or without urge incontinence, usually frequency and nocturia”
  – “sudden desire to pass urine that is difficult to suppress”

• Idiopathic in strictest definition

AUA OAB Guideline 2012

• First Line
  – Behavioral (B)
  – Behavioral + antimuscarinic ©

• Second Line
  – Oral antimuscarinic ER over IR ©

• Third Line
  – InterStim ©
  – PTNS ©
  – Onabotulinum toxinA ©
  – Catheters (expert opinion)
  – Augment (expert opinion)
Unmet Patient Needs in Antimuscarinics

Reasons For First-line Drug Failure

- Insufficient efficacy
- Intolerable side effects
- Dosing convenience
- Other reasons

Perspective of First-line Drug Failure

- Females aged ≤55 years: 57% Insufficient efficacy, 30% Intolerable side effects, 2% Dosing convenience, 9% Other reasons
- Females aged >55 years: 47% Insufficient efficacy, 39% Intolerable side effects, 4% Dosing convenience, 8% Other reasons
- Male: 50% Insufficient efficacy, 24% Intolerable side effects, 3% Dosing convenience, 18% Other reasons
- In employment/activity working: 50% Insufficient efficacy, 31% Intolerable side effects, 7% Dosing convenience, 9% Other reasons
- Retired/unemployment: 50% Insufficient efficacy, 30% Intolerable side effects, 4% Dosing convenience, 14% Other reasons
- OAB dry: 58% Insufficient efficacy, 26% Intolerable side effects, 2% Dosing convenience, 10% Other reasons
- Pure UI: 61% Insufficient efficacy, 24% Intolerable side effects, 3% Dosing convenience, 10% Other reasons
- Mixed UI: 66% Insufficient efficacy, 16% Intolerable side effects, 2% Dosing convenience, 13% Other reasons

Persistence on AM (n=190,000) is 12-40% at 1yr, 8-15% at 2 yrs, 0% (darifenacin) - 16% (trospium) at 3 years!

Source: SSRI, December 2002. US, Europe and Japan,

Veenboer and Bosch  April J Urol 2014
Mirabegron

- β3 adrenergic agonist/K channel opener
- Relaxes detrusor and affects afferents
- No overlapping side effects with antimuscarinics
- First new class of oral agent approved for OAB in decades
- 50 mg once daily, minimal rise HR, intraocular P
Difference from placebo of -0.75 for 50 mg

FDA registration data 4/2012
Difference from placebo of -0.4 at 50 mg

FDA registration data 4/2012
Symphony Study

- 6 combinations mirabegron (25 vs 50mg) and solifenacin (2.5, 5, 10 mg) in 1307 patients 12 wks vs placebo
- Primary outcome mean void volume
- Greater efficacy than solifenacin alone

Abrams J Urol 2013 abs 1958
Posterior Tibial Nerve Stimulation

- Weekly session 8-12 wks. What is minimum?
- Efficacy similar to antimuscarinics with comparator trial with tolterodine
- Side effects minimal
- Unclear PTNS vs Interstim
  - Systemic review showed similar results, no long term data with PTNS
- New studies showing efficacy in Parkinson’s ds and Multiple Sclerosis
• **PTNS**

• 136 reports, 17 studies adequate, 4 good
• Success 54-93% ¹
• Systemic rev of 4 PTNS to sham, 2 PTNS vs antimuscarinic ²
• Pooled subjective success 61% (CI 52-71)
• Pooled objective success 60% (CI 49-74)

Review: Botulinum toxin injections for adults with overactive bladder syndrome
Comparison: 1 Intravesical BTX-A vs Placebo
Outcome: 2 Change in Urinary Frequency

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Botulinum Toxin</th>
<th>Placebo</th>
<th>Mean Difference IV,Fixed,95% CI</th>
<th>Weight</th>
<th>Mean Difference IV,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 4-6 weeks</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Flynn 2009</td>
<td>15</td>
<td>-12.2 (6.4)</td>
<td>-6.8 (6.4)</td>
<td>17.8 %</td>
<td>-5.40 [-11.14, 0.34]</td>
</tr>
<tr>
<td>Ghei 2005</td>
<td>20</td>
<td>-22.5 (12.15)</td>
<td>-14 (12.15)</td>
<td>10.4 %</td>
<td>-8.50 [-16.03, -0.97]</td>
</tr>
<tr>
<td>Sahai 2005</td>
<td>16</td>
<td>-7.51 (4.25)</td>
<td>-1.03 (4.25)</td>
<td>71.8 %</td>
<td>-6.48 [-9.34, -3.62]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>51</strong></td>
<td></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>-6.50 [-8.92, -4.07]</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2 12 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finney 2006</td>
<td>10</td>
<td>-2.18 (2.48)</td>
<td>0.37 (2.48)</td>
<td>67.2 %</td>
<td>-2.55 [-4.72, -0.38]</td>
</tr>
<tr>
<td>Sahai 2005</td>
<td>16</td>
<td>-6.19 (4.62)</td>
<td>-1.14 (4.62)</td>
<td>32.8 %</td>
<td>-5.05 [-8.16, -1.94]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>26</strong></td>
<td></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>-3.37 [-5.15, -1.59]</strong></td>
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Heterogeneity: $\chi^2 = 0.41, df = 2 (P = 0.81); I^2 = 0.0\%$
Test for overall effect: $Z = 5.25 (P < 0.000001)$

Heterogeneity: $\chi^2 = 1.67, df = 1 (P = 0.20); I^2 = 40\%$
Test for overall effect: $Z = 3.71 (P = 0.00021)$

Test for subgroup differences: $\chi^2 = 4.15, df = 1 (P = 0.04), I^2 = 76\%$
Observations

- No ideal dose described
- Efficacy at 2 wks
- Durability range 5-12 mos
- With more injections longer duration
- Elderly and PVR risk retention
- Trigonal injection greater efficacy but higher retention
- UTI 3X higher than placebo suggesting neural involvement in fighting UTIs!
BPH: Not what it seems

• OAB vs BPH?
• Manifestation of metabolic syndrome
• Often associated with erectile dysfunction
• Symptoms tell us who to treat, PSA tells us how to treat
• Size may not matter for sx, but larger more likely BPO and need for Rx
• Inflammation may underlie pathogenesis in part
Over 70 drug combinations for LUTS with BPH

- Guideline
- Cost
- Patient preference
- #1 Familiarity with treatment

ABs

5ARI

PDE5I

AMs

Desmopressin
Meta-Analysis of Combination Trials

Symptom Score

- Placebo: -4
- Combination: -8.2
- Finasteride: -5.5
- α-Blocker: -7.9

Roehrborn '06
<table>
<thead>
<tr>
<th>Nocturia Urgency Frequency</th>
<th>Slow stream</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate &gt;30-60 gm</td>
<td>AB +/- 5ARI</td>
</tr>
<tr>
<td>PVR &gt; 200 cc</td>
<td>AB + 5ARI</td>
</tr>
<tr>
<td>PVR &lt; 200 cc</td>
<td>AB +/- AM +/- DP</td>
</tr>
<tr>
<td>Prostate &lt; 30 gm PSA&lt;1.4</td>
<td>Daily tadalafil</td>
</tr>
<tr>
<td>Age &lt; 50 IF ED......</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Annual Drug Cost</td>
</tr>
<tr>
<td>-----</td>
<td>------------------</td>
</tr>
<tr>
<td>AB</td>
<td>$300</td>
</tr>
<tr>
<td>5ARI</td>
<td>$575</td>
</tr>
<tr>
<td>PDE5I</td>
<td>$1500</td>
</tr>
</tbody>
</table>

Naslund Am J Managed Care ‘06;
Detailed management for persistent bothersome LUTS after basic management

**OAB**
- Storage symptoms
- No evidence of BOO

**Recommended Tests**
- Validated questionnaire
- FVC (frequency/volume chart)

**Optional Tests**
- Flow rate recording
- Residual urine

**Evidence of BOO**
- Shared Decision
- Discuss Options

**Medical Therapy**
- MIST or Surgery Options
  - Flow rate (if not previously used)

**Failure**

**mixed OAB and BOO**

**Predominant BOO**
- Small gland/low PSA²
- Large gland/high PSA²

**Antimuscarinics¹ and alpha blocker or PDE5-I**

**Alpha blocker or PDE5-I and/or 5 ARI**

**Failure**

**Offer MIST or Surgery to patient**

**Clear Obstruction**
- Qmax < 10 mL/sec
- Treat appropriately. If intervention is pursued patients need to be informed of possible higher failure rates

**Pressure flow studies**

**Obstruction?**
- NO
- YES

**Proceed with selected therapy**

McVary AUA
Update 2013
Surgery for BPH

- Indications: Refractory bothersome sx, retention, recurrent UTI, severe hematuria, hydronephrosis, recurrent bladder stones
- TURP - now with bipolar resection and saline
  - Less bleeding and hyponatremia
- Lasers - VLAP with green light 180W vs HoLEP
  - VLAP outpatient, less blood loss, can do on anticoagulated patient
  - ? Durability and late bleed
  - HoLEP long learning curve but for very large prostate best
Sexual dysfunction

- ED as predictor of future MI
  - Greater predictive value than total cholesterol
- 5 PDE5 inhibitors
  - Choose on cost, side effects, time of onset, duration NOT efficacy
  - Avandifil - shortest acting
- ED/BPH and metabolic syndrome
- Premature ejaculation
  - Under recognized
  - SSRIs first step
- Peyronie’s disease
  - Xiaflex (collagenase) injection similar to Duputryns
  - However 10-15% improvement over saline placebo injection
  - Must use penile modeling
• 500% increase utilization from ‘94 to 2000, now 900%
• What is normal T if aging? Using only total T <300 ng/dL
  • 20% 60-70, 30% 70-80, 50% age >80
• Transdermal 5-10 mg q day, Subcutaneous pellets
• No risk of prostate cancer but make sure nl PSA and DRE
• Can use if treated Pca, low risk path
• Risk of CV event- 2 recent reports!
  • 5.9% increased absolute risk, 29% relative risk
• Low serum T and symptoms
  – Low libido, ED, difficulty with ejaculation, decreased penile sensation, reduced well-being, depression, mood swings, impaired cognition, reduced strength, fatigue, anemia, decreased bone density
  – Late onset hypogonadism defined by 3 sexual sx and total T <320 ng/dl and a free <6.4 ng/dL for 3.2% age 60-69 or 5.1% age 60-79 yrs
• Duration of Abx 3 days unless fever then 10-14 day for urologic condition (7 days)
• Growing resistance and recognition of microbiome detrimental effect
• Male- DO NOT GIVE ABX for epididymitis or prostatitis in absence of abnormal UA!
• Young healthy vs older post menopausal female
• Adjunctive measures if >3-6 per year
  – Sexual practices/hygiene
  – Probiotics-lactobacillus
  – ???? Cranberry tablets or drink conflicting data
  – Vaginal estrogen
  – Suppressive antibiotic qhs/post intercourse
    • Nitrofurantoin, trimethoprim, cephalosporin
• **SUI management**
  - Always start with PME or pessary
  - Must document by exam NOT symptoms
  - Durability falls with time
  - Less invasive mid urethral slings initially

• **Use of vaginal mesh**
  - Prolapse use NOT same as mid urethral sling
  - Durability improved with mesh
  - Most prolapse surgery destined to fail at 13 yrs 80%
  - Suspect erosion or infection if
    - Recurrent UTI after
    - Hematuria
    - Dyspareunia
    - Pelvic pain
Nephrolithiasis

- Obesity leading to greater prevalence
- Shift from ESWL to ureteroscopy and laser litho <2cm
- Medical expulsive therapy
  - Tamsulosin cost effective
- Medical evaluation on everyone!
- Prevention
  - Promotes nephrolithiasis
    - Dietary Na
    - Dietary Ca, high ash diets
    - Obesity/lifestyle
  - Inhibits nephrolithiasis
    - Potassium citrate
    - Lemonade
Prostate Cancer- Screening

- Pre-randomization PSA testing
  - 44% (PLCO) vs 3% (Swedish)
- Contamination
  - Powered for 38%
  - 85% had 1 PSA by yr 3
  - 24% in ERSPC
- Non-attendance
  - 15% PLCO, 17% ERSPC
- Difference in PSA testing by randomized arm
  - PLCO 85% vs 85% or 0%
  - ERSPC 83% vs 24% or 59%
Prostate Cancer- Screening

• PLCO (n=76,693) at 13 yrs
  – 1.09 (0.87 to 1.36); 158 vs 145 Pca deaths

• ERSPC (n=162,243) at 11 yrs
  – 0.79 (0.68 to 0.91); 299 vs 462 Pca deaths

• Swedish (n=20,000) at 14 yrs
  – 0.56 (0.39-0.82); 44 vs 78 Pca deaths

• Additional NNT
  – ERSPC 48 by 9 yrs and 33 by 11 yrs
  – Swedish 12 by 14 yrs

After D’Amico 2014
• PSA screening
  – Gain up to 97.1 or loss of up to 20.7 QALY
  – Depends on individual’s utility
  – A utility captures the risk associated with a decision for treatment relative to decision maker’s risk tolerance

• Data support that improved patient education and a shared decision making process could lead to gains in QALY from PSA screening of all men
Influence of Co morbidity

- Minimal or no co morbidity in PLCO 36% (n=26,175)
  - -0.56 (0.33-0.95), p=0.03 22 vs 38 Pca deaths
  - Additional NNT at 5-10 yrs
- Significant co morbidity 64% (n=47,203)
  - -1.43 (0.96-2.11) p=0.08 62 vs 42 Pca deaths
- At 13 yrs interaction of comorbidity and PCSM persisted
  - -0.73 and 1.26 p=0.03

After D’Amico 2014
PLCO
No or minimal Comorobidity
Median Age: 61
NNT = 5

Swedish
All Men
Median Age: 56
NNT = 12

ERSPC
All Men
Median Age: 60.3
NNT = 33
So who should get PSA?

• PSA and PSA change more accurate for PCa in absence of BPH i.e younger men
  – Rise in PSA more the 0.4 on a 5ARI >50% chance Pca!

• PSA benefit in young men in good health

• High risk disease minimizes effect of over diagnosis
• Underutilized
• Gl 3 disease has no molecular characteristics of cancer
• In most men Gl 3+3=6 should probably be strongly offered active surveillance
• Program
  – Initial TRUS bx, PSA q 3 mos
  – Either annual bx or q 3 yrs
  – Multi modal MRI replacing TRUS bx
Prostate Cancer - Localized Disease

- Robotic surgery now over 80% of RRPs
  - Proven lower blood loss, pain, LOS
  - No worse positive margins, BCR, ED or incontinence
  - However learning curve 250-700 cases for plateau in morbidity and outcomes!

- EBRT + ADT (18 mos) vs RRP for high risk PCa
  - No randomized trials until Prospect 2015
  - 3 retrospective series increase CSS for RRP especially higher grade disease
Prostate Cancer- mCRPC

- After LHRH agonist (Lupron, Eligard) or antagonist (Firmagon)
  - Intermittent ADT for no bulky or sx met ds
  - CV risk
  - Always advise baseline DEXA, weights, Ca + Vit D, ? fosamax

- Bicalutamine (Casodex)
- Bicalutamine withdrawl
- Abitaterone (intracellular anti androgen)
- Enzalutamide
- Docetaxel
- Provenge vaccine
- Bone mets
  - Denosunab
  - Radium 223
Bladder Cancer

- 72,000 new cases annually, 27,000 deaths #6 in men
- CIS treated with intravesical immunoRx with BCG
  - Need maintenance for year
  - over 50% will progress to muscle invasive ds
- Muscle invasive treated with radical cystectomy
  - Robot vs open (current trial)
  - 50% after cystectomy develop mets within 2 yrs
  - Standard of care neoadjuvant cisPt based chemoRx
  - No evidence adjuvant chemoRx of benefit
- Metastatic disease
  - OS 12-14 mos
  - CisPt based chemoRx
Renal Cell Ca

- Increasing detection
- More scenarios
  - Bx and observe
  - Lap/open radical nephrectom
  - Open partial nephrectomy
  - Lap/robotic partial NTX
  - Ablate
- Small renal masses < 3cm
  - New trend toward bx
  - Histology/size/growth rate dictates pathway
- Renal sparing surgeries- size, location dependent
  - Ablation
    - Radiofrequency Cryosurgery
    - HiFu
- Chemotherapy with mTor agents
  - Space for each agent unclear
  - Limited survival advantage
• 86% of SRMs <4 cm are low grade
• Avg growth rate 4-6 mm/yr
• 2% of renal tumors under AS metastasized (all >4cm)
• Avg time from detection to met 40mos
Nephrometry Score

1+1+1+p+2=5p
“low complexity”

1+2+3+p+2=8p
“moderate complexity”

3+1+3+a+2h = 9ah
“moderate complexity”

3+2+3+p+3 = 11p
“high complexity”
Cure + Preserve Renal Function

26% of Renal Cell patients have Stage III CKD at diagnosis

CKD worse with RN

OS worse with RN

Speed matters

Lancet Oncol 2006; 7: 735-40

European Urology 64 (2013) 600-606

Fig. 1 – Risk of developing new-onset stage IV chronic kidney disease for patients treated with >25 min versus ≤25 min of warm ischemia. GFR = glomerular filtration rate.
• Know when to hold’em and when to fold’em
• Big data diving is coming and everyone’s outcomes will be public knowledge with new discoveries
• Managing Populations and Cost will reward.....
  – Quality outcomes and use of metrics
  – Safety and use of checklists
  – Earlier diagnosis and biomarkers
  – Prevention will be more important in Urology
    • ED and BPH- reduce obesity/metabolic ds
    • Nephrolithiasis- reduce animal protein and obesity
    • UTIs-make sure correct antibiotic and if needed
    • Earlier dx of prostate, bladder and renal cancers
      – Risk profiles based on FH and lifestyle
      – Improved serum and urinary biomarkers coming
      – Don’t ignore hematuria or assume UTI
      – PSA in correctly chosen man still of benefit but treatment not always necessary